Successful Management With Interferon Alpha-2a After Prednisone Therapy Failure in an Infant With a Giant Cavernous Hemangioma

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A giant cavernous hemangioma of the left arm with severe thrombocytopenia and consumptive coagulopathy was observed in a neonate. Initial treatment with prednisone, platelet transfusions, and clotting replacement failed to control the bleedings. The child was then treated with daily subcutaneous infusions of interferon alpha-2a.Coagulopathy rapidly improved and transfusions were drastically reduced. The hemangioma regressed progressively and disappeared after 4 months of treatment. **Med. Pediatr. Oncol. 28: 213–215** © 1997 Wiley-Liss, Inc.

Key words: giant cavernous hemangioma; Kasabach-Merritt syndrome; medical therapy

INTRODUCTION

Hemangiomas are common in infancy and usually follow a benign course. The spontaneous regression rate is 80–85% [1]. Rarely, they can be giant, produce skeletal overgrowth or high cardiac output failure, or be associated with severe thrombocytopenia, microangiopathic hemolytic anemia, and bleeding. This latter association was described for the first time in a 2-year-old child by Kasabach-Merritt [2] in 1940.

CASE REPORT

A 29-year-old woman (gravida 1, para 1) gave birth at term to a baby girl weighing 3.050 kg. The Apgar score was 7 after the first minute and 9 after the fifth. Postpartum examination revealed a giant hemangioma extending from the left anterolateral chest wall to the middle third of the forearm (Fig. 1). The limb was maintained in extension, and the overlying skin was bluish and intact. She exhibited hematomas and widespread petecchiae over her body. Neither hematuria, nor internal hemorrhages, resulted. The ECG showed right ventricular overload, and the echocardiogram, a mild ventricle enlargement.

Laboratory data revealed a severe consumptive coagulopathy (hemoglobin 7.2 g/dl, platelets 10,000 mm^3, prothrombin time $>$60 sec (n.v. 13–20 sec), partial thromboplastin time 35 sec (n.v. $<$55 sec), fibrinogen undetectable (n.v. 125–300 mg/dl), unconjugated bilirubin 7.2 mg/dl (n.v. $<$12 mg/dl), Coombs' tests were negative). Initial management consisted of platelet and red blood cell transfusions, clotting factors replacement, and corticosteroids (prednisone, 7.5 mg daily). During the following 2 weeks, 12 platelet and eight red blood cell transfusions were administered together with clotting factors replacements, and prednisone 7.5 mg daily, but no significant result was obtained. Her general conditions worsened: the consumptive coagulopathy, thrombocytopenia (platelets 11,000/mm^3) and subsequent anemia (Hb 7.1 g/dl) did not subside. The giant hemangioma and consequent edema did not regress, and a large hematoma (maximum diameter 12 cm) was observed over the left shoulder and laterocervical region.

Interferon alpha-2a therapy was then initiated (3,000,000 U/m^2/day subcutaneously). After the first 10 days of treatment, her general conditions rapidly improved (prothrombin time, 18 sec; partial thromboplastine time, 31 sec; fibrinogen, 156 mg/dl; Hb, 8.2 g/dl; platelets, 12,000 mm^3). The number of transfusions decreased from 28, administered during the first month of life, to eight during the second.

The hemangioma regressed in size, disappearing from the forearm and chest wall after the first month of treatment (Fig. 2). Transfusions and clotting factors replacement were discontinued during the second month of life when laboratory data revealed progressively increasing values that returned to normal (prothrombin time, 13.1 sec; partial thromboplastine time, 28 sec; fibrinogen, 250 mg/dl; Hb, 13.5 g/dl; platelets, 253,000/mm^3) during the following month (Fig. 3). After the fourth month of life, interferon alpha-2a dosage was decreased to 3,000,000 U/m^2 every other day. The hemangioma continued to

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Fig. 1. Giant hemangioma extending from the left anterolateral chest wall to the middle third of the forearm (middle arm and forearm circumference: 23/14 cm, respectively), at birth.

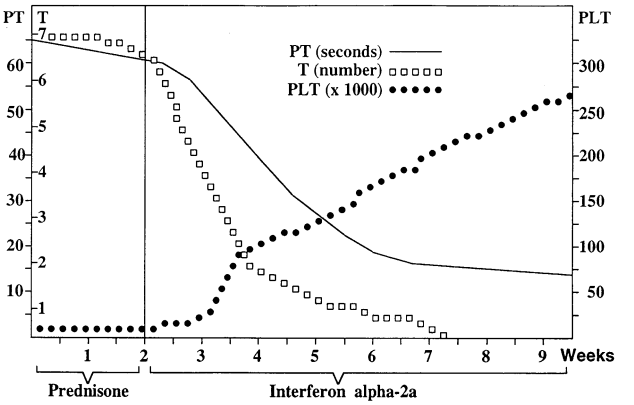

Fig. 3. Laboratory data and transfusions vs. treatment during the first 2 months of life. PT (prothrombine time in seconds), T (number of red blood cell and platelet transfusions), prednisone: 7.5 mg/day; interferon alpha 2a: 3,000,000 U/sqm/day.

Fig. 2. The hemangioma regressed in size, disappearing from the forearm and chest wall after the first month of treatment.

Fig. 4. At present, the left arm is normal, there are no differences in size, color, or function between the two arms; no skeletal overgrowth occurred.

regress until complete disappearance after 4 months of treatment. There were no side effects. During this period, the child's growth was adequate. In accordance with the literature [16], interferon alpha-2a was discontinued after 6 months of treatment. At present, the child is well and no relapse has occurred 26 months after complete remission. The left arm is normal (Fig. 4), there are no differences in size, color, or function between the two arms; no skeletal overgrowth occurred. The regresssion pattern of the hemangioma was followed-up with echo-color Doppler investigations performed every month.

ECHO-COLOR DOPPLER REPORTS

The echo-color Doppler examination is important in the detection of vascular dysplasia, and in distinguishing between venous and artero-venous (A-V) types. Furthermore, with this technique the evolution of the dysplasia can be safely followed-up. In the case reported here, the examination performed on the third day of life showed a giant hemangioma with high and low load A-V shunts located in the anterolateral chest wall, arm, and forearm. Small caliber veins with high velocity flow were also seen. The peripheral venous distribution of the arm was normal. On the fifth day, the situation worsened with the development of edema in the upper limb that compressed the veins. At this point, treatment with interferon was started. Controls performed every month showed a progressive improvement in the ultrasound findings: a progressive reduction of the A-V shunts that gradually disappeared from the chest wall and forearm, an increase in the caliber of veins, and a decrease in venous flow. Finally, the last control revealed a similar arterovenous flow (velocytogram) in the two limbs. Microshunts that had been observed in the proximal region of the cephalic vein, and that had caused an increase in load and venous flow in the cephalic and innominate vein, had also disappeared.

DISCUSSIONS AND CONCLUSIONS

Giant cavernous hemangiomas may cause severe hemorrhages, microangiopathic hemolytic anemia, or signifi-

cant cardiac failure due to arterovenous fistula [2-4]. Various types of therapy for the control and/or cure of these complications have been attempted with different results [5]. Current management of hemangiomas includes drugs (e.g., corticosteroids, aminocaproic acid, and heparin to treat the consumptive coagulopathy, and cyclophosphamide), surgical excision, radiotherapy, and argon laser therapy [6–13]. Surgery is the treatment of choice, but the size and/or anatomic location of the lesion may preclude its removal. Pharmacologic therapy is indicated for inoperable hemangiomas, and for life-threatening complications such as congestive heart failure or bleeding diathesis. Corticosteroids are first-line treatment, and the response rate varies from 30 to 60%.

In patients unresponsive to corticosteroids, treatment is not well defined. A prospective study from the Children's Hospital of Boston evaluated interferon alpha-2a in patients with life-threatening hemangiomas unresponsive to corticosteroids [14–15]. Interferon alpha-2a was used because of its reported inhibition of proliferation of vascular cells [16,17] and minimal side effects [16–20] (e.g., neutropenia, mild fever, and abnormal liver function tests). The response rate was 80% with a mean response time of 7 to 8 months [16]. The pharmacologic effects of interferon alpha-2a remain unclear. It has been shown that endothelial cell proliferation and angiogenesis are inhibited by interferon alpha-2a. The resolution of consumptive coagulation seems related to the decrease in thrombocyte aggregation that may be explained by a reduction in platelet adherence and trapping resulting from the increasing endothelial synthesis of prostacyclin induced by interferon alpha [18–20]. In the case reported here, the reduction in platelet and blood transfusions, the progressive involution in size, and the gradual normalization of the laboratory test values, seem strongly related to interferon administration.

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